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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,256	AZROLAN ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-29* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 15-29 ARE PRESENTED FOR EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on June 21, 2006 after final rejection. Because this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicants' submission, which consisted of an amendment to the specification and claims and an Information Disclosure Statement filed on June 21, 2006 has been entered. Accordingly, the specification at page 1 has been amended and claims 28 and 29 have been added. Also, as reflected by the attached, completed copy of "Substitute for form 1449/PTO", the Examiner has considered the references cited by Applicants.

Specification

The disclosure is objected to because of the following informality:

In the amendment to the specification at page 1, the relationship between U.S. Serial No. 10/313,217, now U.S. Patent No. 6,670,355, and U.S. Serial No. 09/880,295 is indicated to be a continuation. However, the Office records, as well as the Application Data Sheet in U.S. Serial No. 10/313,217, (see page 3 thereof), show that such relationship is a continuation-in-part.

Appropriate correction, which would include an amendment to page 1 of the specification as well as a substitute Application Data Sheet, is required.

Claim Objection

Claim 21 is objected to because of the following informalities:

(i) at line 2, the term "groups" should read as ---group--- because a single Markush group is presented in the claim; and

(ii) at line 5, "an anticoagulants" should read either as ---an anticoagulant--- or ---anticoagulants--- in order to be grammatically correct.

Appropriate correction is required.

Claim Rejection - 35 USC § 112, Second Paragraph, (New Ground)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.", (see MPEP § 2173).

The term "derivative" in the expression "a fibric acid derivative", (line 3), is a relative term which renders the claim indefinite. In particular, "derivative" does not particularly point out the degree or type of derivation that a given compound may have in relation to the parent compound and still be considered a "derivative" as intended by Applicants. Applicants have failed to provide any specific definition for this term in the present specification. Lacking a clear

meaning of the term "derivative", as employed by Applicants, the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter for which Applicant seeks patent protection. Therefore, the identity of those compounds which are intended to be included in or excluded from the present claim would be open to a subjective interpretation and such is inconsistent with the tenor and express requirements of 35 U.S.C. § 112, second paragraph.

Accordingly, the claim is deemed properly rejected.

Claim Rejection - 35 USC § 103

Claims 15-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al. (U.S. Patent No. 5,516,781, cited by Applicants, reference "TT") or Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z"), in view of Schuler et al. (U.S. Patent No. 6,384,046), Somers (U.S. Patent No. 6,121,319, cited by Applicants, reference "XX"), Stedman's Medical Dictionary, ("Stedman's"), Applicants' acknowledgment at page 5, line 10 – page 6, line 22 of the present specification and The Merck Manual of Diagnosis and Therapy ("Merck", cited by Applicants, reference "OOO"), each of record for the reasons of record as set forth in the previous Office action dated December 23, 2005 at pages 3-8, which reasons are here incorporated by reference, as applied to claims 1-27, (which was a typographical error and should have read "15-27" as claims 1-14 had been previously canceled).

Upon review of the above stated rejection, the Examiner has also discovered other typographical errors which are here identified and corrected. In particular, at page 3, second full paragraph, "who teach methods" should read as ---teach methods---; page 4, line 7, "claims 14 and 21" should read as ---claim 21---; page 4, line 3 of the last paragraph, "Given the combined teaches" should read as ---Given the combined teachings---; page 5, line 3, "claims 14 or 21"

should read as ---claim 21---; page 5, paragraph (iii), line 1, ---is effective for treating--- should be inserted after "Morris et al. teach that rapamycin"; page 8, line 3 of the first full paragraph, "did not recognized" should read as ---did not recognize---; and page 8, line 3 of the first full paragraph, "the present claimed subject matter obvious because" should read as ---the presently claimed subject matter unobvious because---. Also, at the section bridging pages 9-10, "Also, the present claims recite the treatment or inhibition of cardiovascular disease or the treatment of atherosclerosis in general...or coronary artery bypass graft.' (col. 1, lines 23-27)" should have been deleted as recognized by Applicants at page 9 of their recent response at the last three lines thereof.

Applicants' remarks at pages 6-9 of their recent response have been carefully considered, but fail to persuade the Examiner of error in his determination of obviousness. Insofar as the present remarks are essentially those of Applicants' response dated September 21, 2005, the Examiner's remarks in response thereto, as presented at pages 6-8 of the previous Office action dated December 23, 2005, and referenced above, are here relied on as being responsive thereto.

Upon further consideration of Applicants' remarks, the Examiner wishes to make the following additional points.

Newly presented claims 28 and 29 are properly included in the claims that are rejected. These claims define species of previous claimed subject matter in that specific active agents that are co-administered with a rapamycin compound have been set forth. The art relied on by the Examiner makes clear that the combination of a rapamycin compound with any of the claimed additional agents, such as a calcium channel blocker and/or an anticoagulant would have been obvious. In particular, see the previous Office action at page 5, paragraph (ii). As a further

motivating factor to combine the active agents taught in the art to be useful for the same purpose, the Examiner newly relies on the teaching in Morris et al. at col. 4, lines 10-22, in particular:

> "This invention also provides a method of using a combination of rapamycin and mycophenolic acid for the same utilities described above. Mycophenolic acid, an antiproliferative antimetabolite, inhibits inosine monophosphate dehydrogenase and guanosine monophosphate synthetase, enzymes in the de novo purine biosynthetic pathway. This results in an inhibition of DNA synthesis which causes an accumulation of cells at the G 1-S interface. Other combinations containing rapamycin that are useful for preventing or treating hyperproliferative vascular disease will be apparent to one skilled in the art. These include, but are not limited to, using rapamycin in combination with other antiproliferative antimetabolites."

It is believed that from the above, one of ordinary skill in the art would have appreciated that combinations of rapamycin and another active agent, which is not necessarily mycophenolic acid could be used.

Also, respecting the identity of an anticoagulant, it appears from Applicants response that they do not take heparin, as disclosed in Mitchell et al., to be such an active agent, (see Applicants' remarks at page 6, line 2 of the penultimate paragraph, "In fact, the teachings of Mitchell (which requires a component not recited in the claims..."). Heparin, however, is a component recited in the claims. As required by present claims 21, 28 and 29, an anticoagulant may be present. This is met by heparin because it is an anticoagulant. In support thereof, see Mitchell et al. at col. 2, lines 53-57, "The authors, showed that the effect of heparin on the injured arterial wall was to inhibit the growth of smooth muscle cells and that this effect was, in no way, related to the anti-coagulant activity of the heparin.". As such, Applicants' position is not well taken.

At page 7 of their response, Applicants have stated that "the prior art does not teach or suggest the use of a rapamycin for the prevention of lipid deposition or accumulation in a vascular wall, *or the treatment or prevention of conditions that are associated with such lipid deposition or accumulation*", (emphasis added). Respecting the emphasized portion of Applicants remarks, the Examiner cannot agree because as presented in the previous Office actions, both primary references, i.e., Morris et al. (U.S. Patent No. 5,516,781) and Mitchell et al. (U.S. Patent No. 5,288,711), expressly teach the treatment of atherosclerosis with rapamycin, (e.g., see Mitchell et al. at col. 3, line 43, "atherosclerosis" and Morris et al. at col. 1, lines 45-60) while atherosclerosis was known to be associated with an accumulation of lipids, (e.g., see Morris et al. at col. 1, lines 51-60, "Atherosclerotic lesions included massive accumulation of lipid laden 'foam cells' derived from monocyte/macrophage and smooth muscle cells" and Steadman's defines atherosclerosis to mean "arteriosclerosis characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries; such deposits are associated with fibrosis and calcification" (page 148, col. 1)). Thus, the art teaches the treatment of a condition, i.e., atherosclerosis, which is associated with lipid accumulation. As such, the art of record clearly speaks to the contrary of Applicants'.

Also, respecting the data at Table 1 of the present specification, Applicants' characterization thereof at page 7 of their response does not diminish the propriety of the present rejection. The data relating to levels of lipids, such as triglycerides and HDL, while supporting the medical use as expressed in claim 1, does not establish any result that would not have been expected for the subject matter that is claimed. At best, such data would refute any position that the presently claimed actives would not be expected to be useful for the claimed purposes.

However, because such a position has not been taken, the data does not have any impact on the present conclusion of obviousness. Insofar as the data relates to the claimed subject matter, (i.e., as Applicants have explained at page 7 of their response, the data was taken from an animal model that is well accepted as a model for human atherosclerosis), such does not persuade the Examiner of error in his determination that the treatment of atherosclerosis would have been obvious because, at the very least, as explained above, the art clearly teaches that rapamycin was known to be effective for the treatment of atherosclerosis.

Accordingly, for the reasons above, which includes the reasons of record, the claims are deemed properly rejected.

Double Patenting

Non-Provisional

I Claims 22-27 and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,680,330, (Zhu et al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z"), already of record, for the reasons of record as set forth in the previous Office action at pages 9-10, as applied to claim 22, which reasons are here incorporated by reference, in further view of Schuler et al., (U.S. Patent No. 6,384,046, already of record) and Somers, (U.S. Patent No. 6,121,319, already of record).

In addition, the patented claims do not specify that other rapamycin derivatives as those in present claims 23-27 could be employed or that a combination of a rapamycin compound with a calcium channel blocker and/or an anticoagulant could be employed.

However, it is believed that one of ordinary skill in the art would have found it to have been obvious to reconcile such differences because the central core of the compound of the '330 patent is the rapamycin core. From this, it is believed that simple derivatives such as those of present claims 23-24, or the specific derivative of present claims 26 and 27 would have been obvious because a person of such skill would have reasonably expected such rapamycin derivative compounds to possess the same activity as the rapamycin compound of the '330 claims. This would have been even more so because such derivative were known to the artisan as also being useful for the treatment of restenosis, (see Morris et al. at col. 3, lines 51-56; Mitchell et al. at col. 3, lines 32-51 and Schuler et al. at the abstract and col. 3, lines 19-22). Also, the patented claims recite "comprising" and thus provide for the presence of additional agents, whether positively recited or not, and agents such as calcium channel blockers and anticoagulants, such as heparin, were known to be useful for also treating restenosis, (i.e., see Somers at col. 6, line 12 and col. 8, line 62 – col. 9, line 6).

Applicants' remarks at pages 9 and 10 of their recent response have been carefully considered, but fail to persuade the Examiner of error in his determination of obviousness. Insofar as the present remarks are essentially those of Applicants' response dated September 21, 2005, the Examiner's remarks in response thereto, as presented at pages 9-10 of the previous Office action dated December 23, 2005, and referenced above, are here relied on as being responsive thereto.

Accordingly, the claims are deemed properly rejected.

II Claims 22-27 and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of U.S. Patent No. 6,432,973, (Zhu et

al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z"), each of record, for the reasons set forth in the previous Office action at page 10-12, as applied to claims 22, 24 and 25, which reasons are here incorporated by reference, in further view of Schuler et al., (U.S. Patent No. 6,384,046, already of record) and Somers, (U.S. Patent No. 6,121,319, already of record).

In addition to those differences already pointed out, the patented claims do not specify that other rapamycin derivatives as those in present claims 23, 26 and 27 could be employed or that a combination of a rapamycin compound with a calcium channel blocker and/or an anticoagulant could be employed.

However, it is believed that one of ordinary skill in the art would have found it to have been obvious to reconcile such differences because the central core of the compound of the '973 patent is the rapamycin core. From this, it is believed that parent rapamycin compound as in present claim 23, or the specific derivative of present claims 26 and 27 would have been obvious because a person of such skill would have reasonably expected such rapamycin compounds to possess the same activity as the rapamycin compound of the '973 claims. This would have been even more so because such derivative were known to the artisan as also being useful for the treatment of restenosis, (see Morris et al. at col. 3, lines 51-56; Mitchell et al. at col. 3, lines 32-51 and Schuler et al. at the abstract and col. 3, lines 19-22). Also, the patented claim recites "comprises" and thus provide for the presence of additional agents, whether positively recited or not, and agents such as calcium channel blockers and anticoagulants, such as heparin, were

known to be useful for also treating restenosis, (i.e., see Somers at col. 6, line 12 and col. 8, line 62 – col. 9, line 6).

Applicants have not included a traversal of the present rejection in their most recent submission. For the reasons above, the claims are deemed properly rejected.

None of the claims are currently in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Raymond J Henley III
Primary Examiner
Art Unit 1614

June 28, 2006